REGION

RESEARCH MAY HELP WITH DOWN SYNDROME

Sanford-Burnham-led study points to a lack of key protein; search is on for effective drug

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Down syndrome's mental disabilities may be caused in large part by lack of an important brain protein, according to a new study led by scientists at the Sanford-Burnham Medical Research Institute.

The study points the way to a possible therapy to improve brain function in children with the genetic abnormality. No such therapy now exists.

Near-normal brain function can be restored in mouse models by increasing levels of this protein, called SNX27, the study found. Researchers have begun searching for drugs that can elevate levels of SNX27, said Huaxi Xu of Sanford-Burnham, the study's senior author.

The study was published Sunday in the journal Nature Medicine. Xin Wang of Sanford-Burnham was the first author.

Lack of SNX27 decreases the number of certain molecules on the surface of mouse neurons, the study found. These molecules, called glutamate receptors, are important for learning.

Researchers studied brain samples collected after death from people with Down syndrome, and found lower levels of SNX27 than in control samples from those without the condition. In addition, neurons of those with Down syndrome have abnormal dendrites, the long filaments that help transmit signals from cell to cell.

If the mouse model is a good guide, restoring the protein should work in children with Down syndrome nearly until puberty. Mice with the equivalent of Down syndrome were tested for such abilities as memory and recognition of new objects. Those treated at the age of one month grew up to test normally, Xu said. A one-month-old mouse is comparable to a 10-year-old child when adjusted for life span, he said.

The mice were treated with gene therapy that delivered a human version of the gene that makes the SNX27 protein. A common virus called an adenovirus was used to insert the gene into the mouse brains. As a result of this single injection, protein production increased, and the mice performed normally on learning tests.

However, gene therapy to alter brain function is at present considered too risky for human use, Xu said, so researchers are looking for a drug that produces the same effect.

Down syndrome produces moderate to severe mental disabilities, along with physical defects of the heart, cataracts and sleep apnea, according to the National Institutes of Health. Those with Down syndrome generally have shorter life spans. Those with milder forms of the condition can live independent lives.

Down syndrome is caused by the presence of three copies of a chromosome, a condition called trisomy, instead of the usual two, one from each parent. The specific chromosome involved is called chromosome 21. Mice bred with the equivalent trisomy also exhibit learning disabilities.

Researchers have previously found that an extra chromosome 21 could repress activity of genes on other chromosomes. But this study is the first to specifically implicate SNX27 and discover a mechanism for action, Xu said.

Among its other functions, chromosome 21 produces a certain kind of microRNA, which are small snippets of RNA that regulate gene function. This microRNA, called mir-155, suppresses SNX27. So reducing the level of mir-155 should result in higher levels of the SNX27 protein.

"One way to do this would be to use antisense RNA to bring down this mir-155," Xu said.